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Hyperkalaemia: aetiology, epidemiology, and clinical significance

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Disturbances in the potassium homeostasis are common among patients with heart failure (HF) and negatively affect clinical outcome. Patients with HF have a higher prevalence of common risk factors related to hyperkalaemia, including diabetes mellitus, hypertension, and chronic kidney disease. Furthermore, the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, is an important risk factor for developing hyperkalaemia. The association between hyperkalaemia and mortality is not unequivocal, depends on the study type (trial vs. real-world setting) and is often confounded. More importantly, hyperkalaemia is an important cause of discontinuation or failure to uptitrate to guideline recommended dosages of RAAS inhibitors, which in turn may negatively impact clinical outcomes. The goal of this review is to discuss the epidemiology, aetiology, and clinical consequences of potassium disturbances in HF.

Introduction

Potassium levels are often routinely measured in patients with heart failure (HF) and HF guidelines recommend frequent measurement of potassium during hospitalization for HF.[1] In the general population, disturbances in potassium homeostasis are associated with (insulin dependent) diabetes, chronic kidney disease, hypertension and use of renin-angiotensin-aldosterone system (RAAS) inhibitors, as well as diuretics.[2–4] Hyperkalaemia is associated with worse outcomes in patients with HF as well as with discontinuation or a reduction of RAAS inhibitors, which may impact survival.[5–8] Therefore, hyperkalaemia warrants specific attention. This is even more relevant due to the emergence of new treatment possibilities including novel potassium binding agents.[9] This review summarizes the aetiology, epidemiology, and clinical consequences of hyperkalaemia in HF.

Clinical causes and aetiology of hyperkalaemia

Hyperkalaemia is an often observed and potentially dangerous event in patients with HF. Yet, in patients with HF, volume overload and activation of the RAAS will lead to potassium excretion and sodium reabsorption in the proximal tubule of the kidney, which suggests that patients with HF have a tendency for lower potassium levels. Then why is hyperkalaemia an often-observed event in patients with HF? Hyperkalaemia is caused by a complex interplay of both environmental as well as physiological factors. Predictors of hyperkalaemia in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) program included age $\geq$75 years, male gender, diabetes, creatinine $\geq$2.0 mg/dL, and background use of angiotensin-converting enzyme (ACE) inhibitors or spironolactone. Furthermore, candesartan increased the risk of hyperkalaemia from 1.8% in placebo to 5.3%, however, in this *post hoc* analysis no strict threshold for hyperkalaemia was defined as the definition of hyperkalaemia as an

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adverse event was determined by the treating physician.[7] These findings were confirmed in other randomized controlled trials including the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, the Trial of Intensified vs. Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF), in a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials and in a more recent example of a real-world population from the BIOSTAT-CHF study, (*Figure 1*).[8,10-12] Particularly in the BIOSTAT-CHF study, the prevalence of hyperkalaemia showed a distinct geographical distribution independent of risk factors for developing hyperkalaemia including age, sex, usage of RAAS inhibition, and the presence of diabetes mellitus and hypertension, suggesting possible differences in potassium monitoring as well as clinical practice across Europe (*Figure 2*).[10]

In physiological conditions, potassium is sequestrated from the plasma, creating an equilibrium between potassium intake and excretion. Two processes are key, first the Na^+/K^+ ATPase pump is important for exchanging intracellular Na^+ for extracellular K^+.[5,13-15] This process is of particular importance in stress situations under the influence from the sympathetic nervous system through beta-2-receptors as well as insulin, where cellular uptake of potassium is increased following an increased potassium load.[16] Following, potassium homeostasis is established mostly by excretion of potassium via urine. This also explains the key importance of renal function in potassium homeostasis. In physiological circumstances, potassium is filtered through the glomerular capillaries and excreted by the distal collecting duct. This process is highly dependent on adequate function of the RAAS and renal perfusion as well as sodium availability to the distal nephron.[15] Hence, disturbance of the RAAS, reduction of renal perfusion and reduction in sodium availability are all risk factors for hyperkalaemia.

In the case of HF all these processes are disturbed: the RAAS is up-regulated, renal perfusion is reduced and sodium is often excreted due to usage of diuretics. Particularly in diabetics, the elderly, and patients on RAAS inhibition, aldosterone production is reduced.[17,18] Additional age dependent reduction in the availability of nephrons further increases the risk for hyperkalaemia.[19] In addition, beta-blockers are also associated with a decreased cellular uptake of potassium by inhibition of the sympathetic nervous system, which increases the risk for a hyperkalaemic event.[16] The association between hypertension and hyperkalaemia is characterized by pseudohypoaldosteronism, renal tubular unresponsiveness to aldosterone, which leads to hyperkalaemia and metabolic acidosis.[20] However, the association between hypertension and hyperkalaemia in HF is not unequivocal and previous reports might have been confounded by renal function and medication use.

Incidence and prevalence of hyperkalaemia in heart failure

The overall reported incidence of hyperkalaemia differs depending on the study setting (trial vs. registry) and

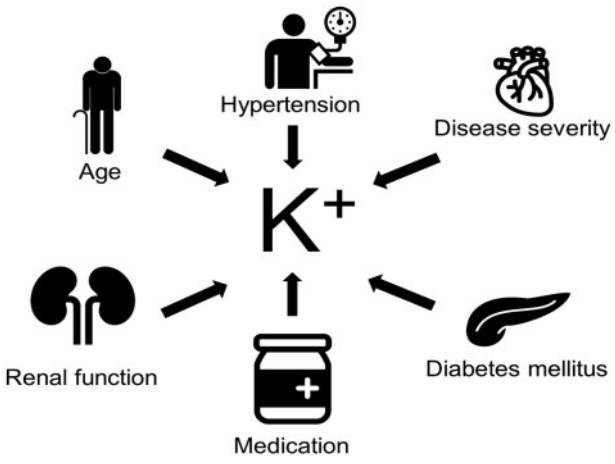

Figure 1 Factors in patients with heart failure associated with hyperkalaemia.

severity (acute vs. chronic) of HF. Among clinical trials involving RAAS inhibitors as a monotherapy, the incidence of hyperkalaemia ranges from 3% to 7% (*Figure 3*). In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), incidence rates of hyperkalaemia were almost double (7.1% vs. 4.0%) in the group treated with enalapril compared with placebo during a mean 188 days follow-up.[21] In the SOLVD trials, where patients were also randomized to either placebo or enalapril, the incidence rates of hyperkalaemia during a mean follow-up of 2.7 years were 6% in the treatment group and 4.2% in the placebo group.[12,22] When a definition of 6.0 mEq/L was used as a definition of hyperkalaemia, the incidence rate in the treatment group dropped to 1.1%.[12,22] Nevertheless, the incidence in the SOLVD and CONSENSUS trials are largely underestimating contemporary rates of hyperkalaemia, as both trials were performed in an era where no other background RAAS inhibition was prescribed.[22] In the results of Candesartan in Heart failure-Assessment of moRtality and Morbidity (CHARM) alternative trial, where 2258 patients intolerant to ACE inhibitors were randomized to candesartan or placebo, incidence hyperkalaemia (>6.0 mEq/L) was 3% compared with 1.3% in the placebo group during a median follow-up of 33.7 months. Here, hyperkalaemia was defined as a potassium level of >6.0 mEq/L.[23] When candesartan was added to treatment with background ACE inhibition in the CHARM-Added trial, overall incidence rates of hyperkalaemia were 3% in the treatment arm compared with 1% in the placebo arm during a 41 months median follow-up time.[24] The relatively lower incidence rates of hyperkalaemia in the treatment arm of the CHARM-added trial (3% in 41 months median follow-up) compared with the CHARM-alternative trial (3% in 33.7 months median follow-up), can potentially be explained by differences in the study population. Patients included in the CHARM-alternative trial had a higher prevalence of background treatment with spironolactone (25% in CHARM-alternative vs. 17% in CHARM-added), which based on previous results from a follow-up to the RALES trial is an important risk factor for developing hyperkalaemia when additional RAAS inhibition is added.[23-25]

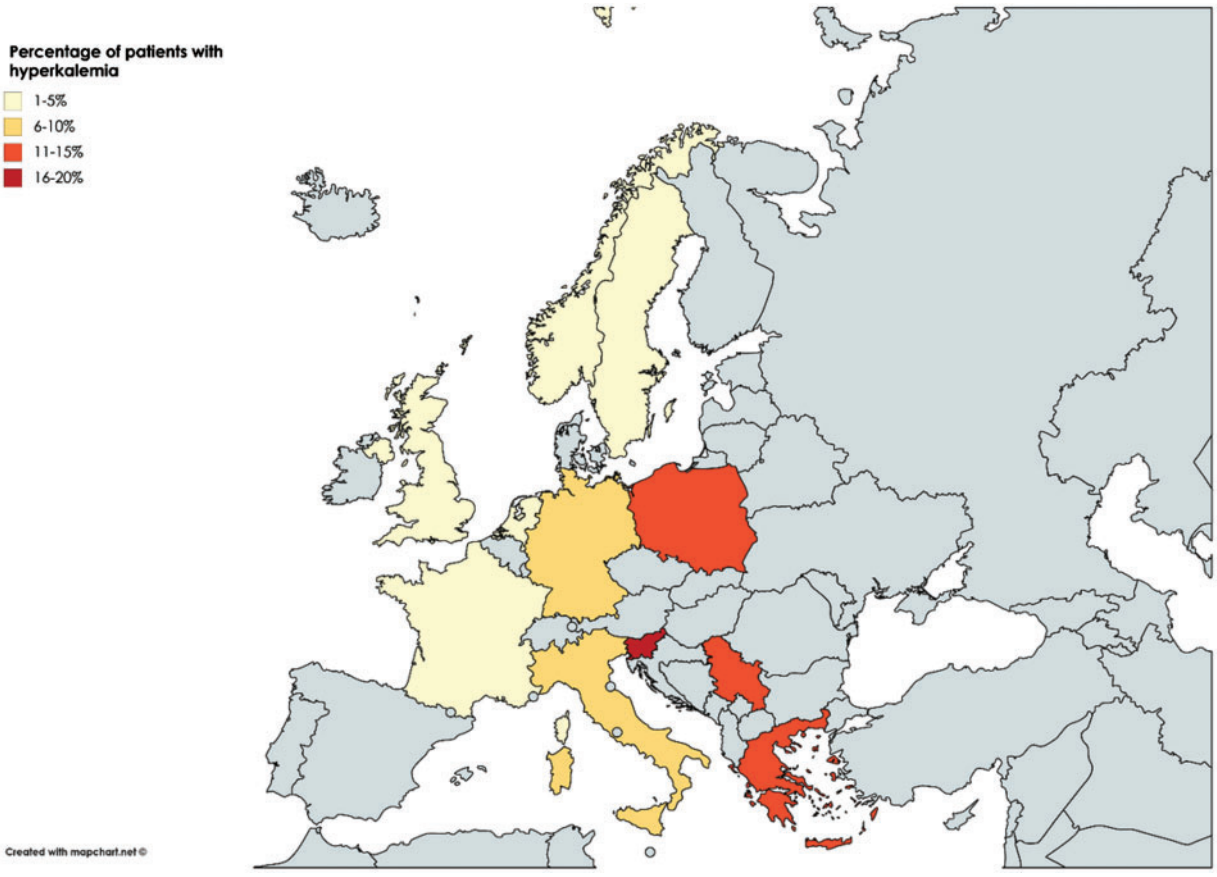

Figure 2 Differences in prevalence of hyperkalaemia across Europe (reproduced with permission from de Denus *et al.*[12]).

In trials involving aldosterone inhibition, overall incidence rates of hyperkalaemia were on average higher. In the EMPHASIS-HF study, where 2737 patients were either randomized to the MRA eplerenone or placebo, incident hyperkalaemia (>5.5 mEq/L) was 8.0% in the treatment group compared with 3.7% in the placebo group.[8,26] However, the incidence rate of hyperkalaemia in this study is probably underestimated as patients with potassium levels >5.0 mEq/L were excluded at study inclusion.[26] In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), 6632 patients with acute myocardial infarction complicated by left ventricular dysfunction and HF, incidence rates of hyperkalaemia were 15.6% in the patient group treated with eplerenone vs. 11.2% in the placebo group during a 16 month mean follow-up, but again similar to the EMPHASIS-HF trial, patients with potassium of >5.0 mEq/L were excluded.[27] In contrast to the EMPHASIS-HF and EPHESUS trials, the Randomized Aldactone Evaluation Study (RALES) reported rates of hyperkalaemia (>6.0 mEq/L) with 2% in the study group treated with spironolactone vs. 1.4% in the placebo group during a follow-up of 24 months.[28] The overall incident rates of hyperkalaemia seemed lower in the RALES trial due to the stricter definition of hyperkalaemia (>6.0 mEq/L) and the lower prevalence of background RAAS inhibition by ACE inhibitors/angiotensin II receptor blockers (ARB).[26-28] The fact that this considerably influenced incidence rates of hyperkalaemia is further supported by a follow-up study, which showed that after the introduction of spironolactone on top of treatment with ACE inhibitors, the rate of hospitalization for hyperkalaemia rose from 2.4 per 1000 patients in 1994 to 11.0 per 1000 patients in 2001.[25]

A more recent study is the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study, which saw 8399 patients randomized to either entresto or enalapril in addition to recommended therapy. Incidence rates were considerably higher in this trial compared with previous trials involving RAAS inhibition, incidence rates of hyperkalaemia were similar between patients treated with entresto (16.1%) and enalapril (17.3). When using a more stringent definition of >6.0 mEq/L, patients treated with entresto (4.3%) had lower incidence rates ($P = 0.007$) of hyperkalaemia compared with patients treated with enalapril (5.6%).[29] The fact that concomitant usage of entresto on top of background therapy can reduce the risk for incident hyperkalaemia, particularly in patients treated with background MRA, is further supported by a recent *post hoc* analysis of the PARADIGM-HF trial.[30]

In trials with HF patients with preserved ejection fraction (HFpEF) incidence rates of hyperkalaemia are arguably lower (*Figure 3*).[31-33] In the CHARM-preserved trial, where patients with HFpEF were randomized to candesartan or placebo, incidence rates of hyperkalaemia (defined as >6.0 mEq/L) were 2% in both groups during a median follow-up of 36.6 months.[32] In the Irbesartan in HF patients

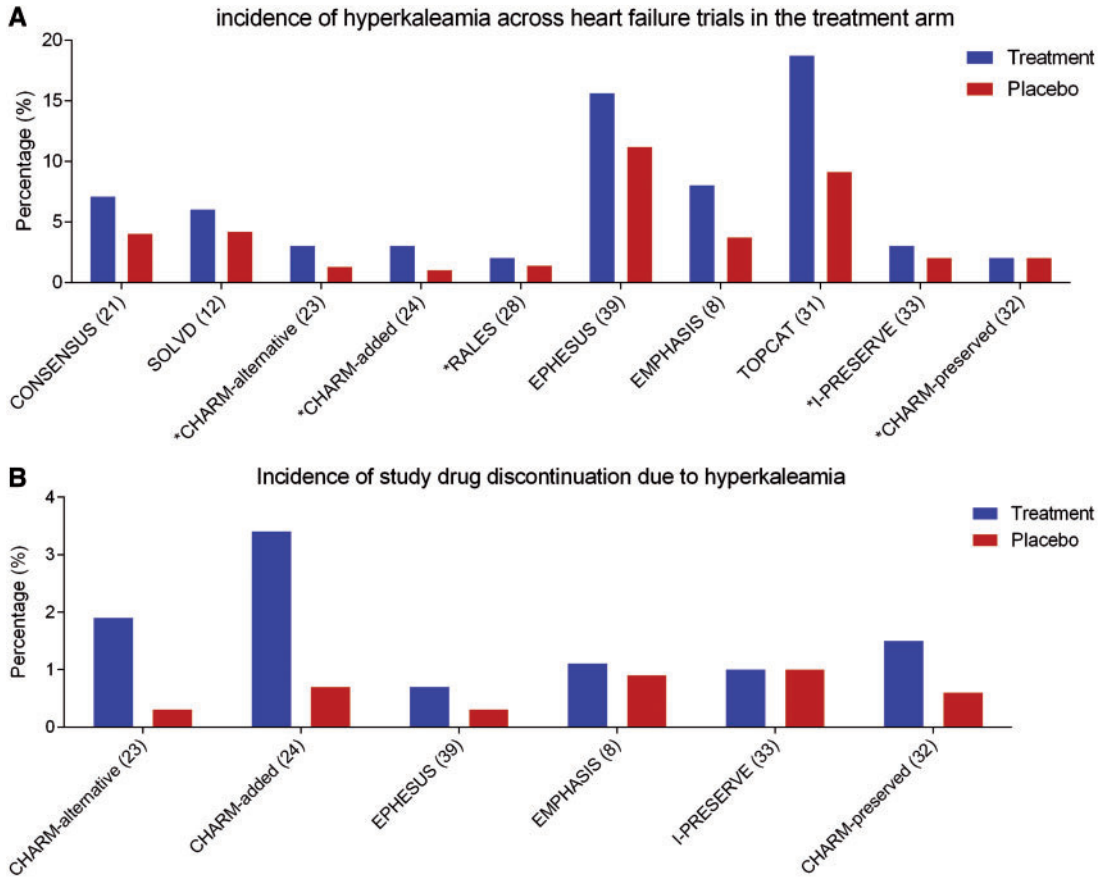

Figure 3 Prevalence of hyperkalaemia across heart failure trials (*A*). Discontinuation of study drug due to hyperkalaemic events across heart failure trials (*B*). Asterisk (*) denotes a definition of hyperkalaemia as >6.0 mEq/L.

with a preserved ejection fraction (I-PRESERVE) trial, incidence rates of hyperkalaemia (defined as >6.0 mEq/L) were slightly higher in the treatment group (3%) vs. the placebo group (2%, $P = 0.01$), however, this did not lead to more drug discontinuation.[33] In the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, patients from the Americas with HFpEF treated with spironolactone had higher incidence rates of hyperkalaemia (18.7%) compared with placebo (9.1%) during a follow-up of 3.3 years.[31,34] Although also here, similar to the Mineralocorticoid receptor antagonist (MRA) trials in patients with HF with reduced ejection fraction (HFrEF), patients with HFpEF and a potassium of ≥5.5 mEq/L within the 6 months prior or ≥5.0 mEq/L in 2 weeks prior to randomization were excluded.[31]

Among patients with acute HF, hyperkalaemia occurred in 7.8% of patients treated with tolvaptan and 6.6% of patients treated with placebo in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial.[35] In a cross-sectional *post hoc* analysis from the Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion (PROTECT) trial, hyperkalaemia occurred only in 1% of overall study participants with no difference between study drug and placebo.[36] However, patients with potassium <3.0 mEq/L at admission were excluded from this study, so the overall prevalence could be lower in a real-world setting. Similarly, only 3% of patients in the Coordinating Study Evaluating Outcomes of Advising and Counseling Failure (COACH) trial showed potassium levels >5.5 mEq/L.[36] However, in both these studies only cross-sectional measurements of potassium were taken into account.

Clinical consequences of hyperkalaemia

Hyperkalaemia has two important clinical consequences. The first one is a direct effect on clinical outcomes by causing possible fatal arrhythmias. The second clinical consequence of hyperkalaemia is discontinuation or down titration of key HF drugs, which may indirectly affect clinical outcomes.

Whether potassium is an independent risk factor for outcome or a consequence of other risk factor remains unclear.[5,35-38] A follow-up study after publication of the RALES trial reported an increase in hyperkalaemia related mortality.[25] In acute HF, *post hoc* analyses from the PROTECT, COACH, and EVEREST trials potassium levels at admission or a change of potassium levels during hospitalization did not show a significant association with post-discharge survival.[35,36] Similarly, hyperkalaemia was not associated with increases in mortality in both the EPHESUS and EMPHASIS-HF trials.[8,39] The fact that hyperkalaemia was not associated with increased mortality in many of

these trials can potentially be explained by the controlled settings in which these trials took place. Indeed, potassium was routinely monitored in these trials and overall tightly controlled, hence very high potassium levels (>6.0 mEq/L) were relatively rare in these trials. Further proof for this is provided by two recent real-world studies, which showed a significant association between hyperkalaemia and an increased mortality.[40,41] In the first study, Núñez *et al.*[40] showed that among 2164 patients with a total of 16 116 potassium observation measured at every physician-patient encounter (including hospital admissions and ambulatory settings) hyperkalaemia (>5.0 mEq/L) was associated with an increased mortality. Similarly, in a study by Aldahl *et al.*[41] among 19 549 patients with HF, hyperkalaemia was associated with increase mortality rates. In a very recent individual-level data meta-analysis of 27 international cohorts from the general population, both hypo- and hyperkalaemia was associated with more adverse outcomes.[42] In these real-world studies the overall distribution of potassium levels was wider compared with trial, which suggests an increased mortality risk of hyperkalaemia potentially occurs at higher potassium levels compared with the conventional >5.0 mEq/L or >5.5 mEq/L threshold.[41]

The second and perhaps most important clinical consequence of hyperkalaemia is discontinuation of lifesaving medication for HF. Indeed, in both the CHARM-alternative as well as the CHARM added trials, the study drugs were discontinued in respectively 1.9% and 3.4% of participants, which were higher rates compared with the placebo arm.[23,24] Also, in the EPHESUS and EMPHASIS studies, eplerenone was discontinued in 0.7% and 1.1% of patients.[26,27] Perhaps most importantly, the occurrence of hyperkalaemia did not affect the survival benefit of RAAS inhibitors.[6–8,39] Further proof for this was provided in a real-world study from the BIOSTAT-CHF study group.[10,43] In this study, potassium levels were measured as part of the study protocol in 1666 patients with HF and a reduced ejection fraction. Patients were sub-optimally treated at baseline. The authors showed that higher levels of baseline potassium were independently associated with lower uptitration rates of RAAS inhibition after 3 months of the study. Furthermore, we showed that there was no significant interaction between potassium or a change in potassium and the beneficial effects of uptitration to guideline recommended levels of RAAS inhibition.[10]

Conclusion

Concluding, a combination of a higher prevalence of risk factors including diabetes mellitus, older age, renal failure, hypertension, and usage of medication that increases potassium levels, put patients with HF at considerable risk for hyperkalaemia. Hyperkalaemia is potentially associated with adverse clinical outcomes and might lead to reductions or even discontinuation of RAAS inhibitors. Taken together, this warrants closer monitoring of potassium levels. Furthermore, novel potassium binding agents might be useful in patients with HF and may allow for more adequate uptitration of RAAS inhibitors, which in turn can have an impact on clinical outcomes in these patients.[9,44–46]

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